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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/710,058	11/10/2000	David Anderson	RIGL-011	4112

83092 7590 01/22/2009

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ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
01/22/2009	PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DAVID ANDERSON and BEAU PEELE

Appeal 2008-2576
Application 09/710,058
Technology Center 1600

Decided: January 22, 2009

Before DONALD E. ADAMS, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1-3 and 20-22, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to a retroviral vector (claims 1, 2, and 20) and a mammalian cell comprising a retroviral vector (claims 3, 21 and 22). Claims 1 and 20 are illustrative:

1. A retroviral vector comprising a polynucleotide encoding a green fluorescent protein (GFP) having the amino acid sequence of SEQ ID NO: 2.

20. A retroviral vector of claim 1 or 2, wherein the polynucleotide comprises a human codon-optimized nucleic acid encoding a Renilla GFP.

The Examiner relies on the following evidence:

Zolotukhin	US 5,874,304	Feb. 23, 1999
Bryan	US 6,232,107 B1	May 15, 2001

M.T. Anderson et al., "Simultaneous fluorescence-activated cell sorter analysis of two distinct transcriptional elements within a single cell using engineered green fluorescent proteins," 93 *Proc. Natl. Acad. Sci. USA* 8508-8511 (1996).

Marti F.A. Bierhuizen et al., "Green Fluorescent Protein Variants as Markers of Retroviral-Mediated Gene Transfer in Primary Hematopoietic Cells and Cell Lines," 234 *Biochem. Biophys. Res. Comm.* 371-375 (1997).

Josep M. Aran et al., "Construction and characterization of bicistronic retroviral vectors encoding the multidrug transporter and β-galactosidase or green fluorescent protein," 5(4) *Cancer Gene Therapy* 195-206 (1998).

Appellants rely on the following evidence:

Linzhao Cheng et al., "Use of green fluorescent protein variants to monitor gene transfer and expression in mammalian cells," 14 *Nature Biotechnology* 606-609 (1996).

John P. Levy et al., "Retroviral transfer and expression of a humanized, red-shifted green fluorescent protein gene into human tumor cells," 14 *Nature Biotechnology* 610-614 (1996).

Yutaka Hanazono et al., "Green Fluorescent Protein Retroviral Vectors: Low Titer and High Recombination Frequency Suggest a Selective Disadvantage," 8 *Human Gene Therapy* 1313-1319 (1997).

The rejections presented by the Examiner are as follows:

1. Claims 1-3 and 20 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Bryan and Aran.

2. Claim 20 stands rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Aran, Bryan and Zolotukhin.

3. Claims 1-3 and 20 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Zolotukhin and Bryan.

4. Claims 1, 3, and 20-22 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Bierhuizen and Bryan.

5. Claims 1-3 and 20-22 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Bierhuizen, Bryan and Aran.

6. Claims 1, 3, and 20-22 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Anderson and Bryan.

We affirm all the rejections presented by the Examiner.

ISSUE

Is detectable fluorescence in a mammalian cell necessary to render the claimed invention prima facie obvious to a person of ordinary skill in the art at the time the invention was made in view of the combination of references relied upon by the Examiner?

FINDINGS OF FACT (FF)

1. Claim 1 is drawn to a retroviral vector comprising a polynucleotide encoding a green fluorescent protein (GFP) having the amino acid sequence of SEQ ID NO: 2. There is no requirement in Claim 1 that the claimed retroviral vector be capable of expressing GFP in a manner that results in fluorescence in a host cell. There is also no requirement in Claim 1 that the retroviral vector be used to produce a stable cell line that expresses a green fluorescent protein (GFP) having the amino acid sequence of SEQ ID NO: 2.

2. Appellants concede that "the amino acid sequence of wild-type *Renilla* GFP was known prior to" the filing date of the present invention (App. Br. 7). The Examiner finds that Bryan "teaches protein Seq. Id. No. 16 which corresponds (e.g., has **100% sequence identity**) to 'wild type' Renilla GFP of **Seq. Id. No. 2**, as recited in the instant Claim 1" (Ans. 4-5). Bryan teaches that

> It would be desirable to have a variety of . . . fluorescent proteins, particularly, Renilla GFP available rather than use muteins of *A. Victoria* GFP. . . . It would also be desirable to have a variety of GFPs . . . available in order to optimize systems for particular applications and to improve upon existing methods.

(Bryan, col. 5, ll. 12-19.)

3. Appellants concede "that retroviral vectors containing <u>altered</u> *Aequoria* GFP were well known and had been successfully used prior to filing their patent application" (App. Br. 7). Aran teaches retroviral vectors comprising "a humanized, red-shifted gene fluorescent protein (GFP) from jellyfish

Aequorea Victoria" (Aran 195: Abstract and 196: col. 1, ll. 5-15). Aran teaches that Cheng and Levy

> have recently shown efficient expression of a humanized, red-shifted GFP when introduced through retroviral vectors into different cell types. Our vector, similar to their vectors, included an improved version of GFP. The two new features of this second-generation GFP are a S65T gain of function mutant, which results in a red-shifted excitation peak with increased brightness, and the conversion of jellyfish GFP codons to human codon usage, which results in higher expression levels because of a more efficient translation in mammalian cells. Using the humanized, red-shifted GFP, a single copy of the integrated viral genome has been shown to be sufficient for production of detectable fluorescence.

(Aran 204: col. 1, ll. 1-15; *see also* Cheng 606: Abstract and Levy 610: Abstract.) Cheng teaches a retroviral vector comprising *Aequorea Victoria* GFP (Cheng 606: Abstract). Levy teaches a retroviral vector comprising *Aequorea Victoria* GFP (Levy 610: Abstract). Bierhuizen teaches "retroviral vectors containing the *Aequorea Victoria* green fluorescent protein (GFP) gene and improved versions thereof" (Bierhuizen 371: Abstract and 373: Fig. 2A). Anderson teaches retroviral vectors comprising *Aequorea Victoria* GFP (Anderson 8509: col. 1, ll. 44-58). Anderson teaches GFP variants "including the S65T and V163A mutations (termed GFP-Bex1)" (Anderson 8509: col. 1, ll. 59-60). Anderson reports that their "studies show that GFP-Bex1 . . . have sufficient fluorescence signal to be readily detected by FACS, and that both variants can be quantitatively detected independently, permitting their simultaneous detection at the single cell level" (Anderson 8510: col. 2, l. 50 - 8511: col. 1, l. 2). Zolotukhin teaches retroviral vectors comprising *Aequorea Victoria* GFP (Zolotukhin,

col. 2, ll. 31-33 and col. 6, ll. 11-14). Zolotukhin teaches "synthetic and 'humanized' versions of green fluorescent protein (GFP) genes adapted for high level expression in mammalian cells, especially those of human origin. Base substitutions are made in various codons in order to change the codon usage to one more appropriate for expression in mammalian cells" (Zolotukhin Abstract). Zolotukhin teaches that "[c]ertain GFP variants have recently been reported that have improved spectral properties[, specifically] . . . a Ser 65 → Thr GFP mutant that has a spectrum much closer to that of *Renilla reniformis*, which has an extinction coefficient per monomer more than 10 times that of the longer-wavelength peak of Aequorea GFP" (Zolotukhin, col. 1, ll. 60-67). Hanazono teaches a retroviral vector comprising *Aequorea Victoria* GFP (Hanazono 1313: Abstract and col. 2, ll. 2-3).

4. Bryan teaches that *A. Victoria* GFP "is not ideal for use in analytical and diagnostic processes. Consequently [*A. Victoria*] GFP mutants have been selected . . . a stated purpose in constructing such [prior art] mutants has been to attempt to make the *A. Victoria* GFP more like the GFP from Renilla" (Bryan, col. 4, ll. 53-60). Appellants concede "that the superior spectral properties of wild-type *Renilla* GFP were well known prior to filing their patent application" (App. Br. 7).

5. Bryan teaches

> [v]ectors containing DNA encoding a Renilla . . . GFP are provided. In particular, expression vectors that contain DNA encoding a Renilla . . . GFP linked in operational associated with a promoter element that allows for the constitutive or inducible expression of Renilla . . . GFP are provided. Native Renilla GFP has been expressed.

(Bryan, col. 9, ll. 17-23.)

Bryan also teaches that the *Renilla reniformis* gene "can be modified by substitution of codons optimized for expression in selected host cells or hosts, such as humans and other mammals" (Bryan, col. 5, ll. 44-46).

6. The Examiner finds that Bryan fails "to *explicitly teach* the use of a retrovirus as a vector" (Ans. 5). However, Bryan teaches that "[a]ppropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells . . . [including] those which integrate into the host cell genome" (e.g., a retrovirus) (Bryan, col. 23, l. 65 - col. 24, l. 2). In this regard, the Examiner finds that Bryan teaches the use of expression systems involving promoters within "**retroviral** long-terminal repeats" (Ans. 6; *Cf.* Bryan, col. 60, l. 29).

7. Bryan teaches the use of *Renilla mulleri* GFP in a variety of different applications ranging from "diagnostic systems for the in vivo detection of neoplastic tissues" to novelty items "designed for entertainment, recreation and amusement, and include, but are not limited to: toys, particularly squirt guns, toy cigarettes, toy 'Halloween' eggs, footbags and board/card games; finger paints and other paints, [etc.]" (*see generally* Bryan, col. 7, l. 51 - col. 8, l. 39).

8. Claim 20 is drawn to a retroviral vector of Claim 1 or 2, wherein the polynucleotide comprises a human codon-optimized nucleic acid encoding a *Renilla* GFP.

PRINCIPLES OF LAW

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness

based upon the prior art." *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). On appeal to this Board, Appellants must show that the Examiner has not sustained the required burden. *See* (1) *Ex parte Yamaguchi*, http://www.uspto.gov/web/offices/dcom/bpai/ prec/fd074412.pdf, slip op. at 5 and 23 (BPAI Aug. 29, 2008) (precedential); (2) *Ex parte Fu*, http://www.uspto.gov/web/offices/ dcom/bpai/prec/fd080601.pdf, slip op. at 5 and 20 (BPAI Mar. 31, 2008) (precedential); (3) *Ex parte Catan*, http://www.uspto.gov/web/ offices/dcom/bpai/prec/fd070820.pdf, slip op. at 3 and 21 (BPAI Jul. 3, 2007) (precedential), and (4) *Ex parte Smith*, http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf, slip op. at 4, 9 and 23 (BPAI Jun. 25, 2007).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, ___ 127 S. Ct. 1727, 1739 (2007).

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103.

Id. at 1742. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 127 S.Ct. at 1741. *See also id.* at 1742 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). "In determining whether obviousness is established by combining the teachings of the prior art, the

test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii) ("Any arguments or authorities not included in the brief or a reply brief ... will be refused consideration by the Board, unless good cause is shown.").

ANALYSIS

Initially, we recognize Appellants' reliance on the teachings of Aran, Hanzano, Levy, Cheng and Anderson. All of these references relate to *Aequorea Victoria* GFP (FF 3). Nevertheless, Appellants assert that "Aran states that wild type GFP fluorescence was 'undetectable'"; "Hanzano states that their attempts to isolating wild-type GFP-expressing lines 'failed'"; "Levy states that 'wildtype GFP could never be visualized'"; "Cheng states that wild type GFP expression 'failed'"; and "Andersen [sic] states that fluorescence was 'not sufficient to resolve infected from uninfected cells'" (App. Br. 8 (footnotes removed)). In sum, Appellants contend that "these references . . . *teach away* from what is being claimed". We disagree.

Appellants state that "Claim 1 is illustrative of all of the appealed claims" (App. Br. 5). There is no requirement in Claim 1 that (1) the claimed retroviral vector be capable of expressing GFP in a manner that results in fluorescence in a host cell or (2) the retroviral vector be used to produce a stable cell line that expresses a green fluorescent protein (GFP) having the amino acid sequence of SEQ ID NO: 2 (FF 1).

Further, Appellants recognize "that successful expression of [*Aequorea Victoria*] GFP using a retroviral vector *required* altering the

amino acid sequence of the GFP" (App. Br. 8). The GFP protein having the amino acid sequence of SEQ ID NO: 2 is not an *Aequorea Victoria* GFP, instead it is a *Renilla* GFP (FF 2).

With regard to *Aequorea Victoria* GFP mutants, Bryan teaches that "a stated purpose in constructing such [prior art] mutants has been to attempt to make the *A. Victoria* GFP more like the GFP from Renilla" (FF 4). Therefore, the prior art recognized that in order to obtain fluorescence of *A. Victoria* GFP in a host cell, a person of ordinary skill in the art would have to modify the *A. Victoria* GFP to make it more like *Renilla* GFP. Accordingly, the preponderance of the evidence on this record supports a conclusion that a person of ordinary skill in the art at the time this invention was made would have reasonably expected that a retrovial vector expressing *Renilla* GFP would produced detectable fluorescence in the host cell. "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d at 1581 (internal quotations omitted). Accordingly, we are not persuaded by Appellants' contention to the contrary.

Bryan and Aran:

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative (FF 1).

Based on the combined teachings of Bryan and Aran (FF 2-7) the Examiner concludes that

> it would have been obvious to one of ordinary skill in the art at the time of appellant's [sic] invention to select a retroviral vector for use in a cellular host . . . with use of a genetic

> construct comprising a polynucleotide (e.g., cDNA) encoding a wild-type Renilla green fluorescent protein (GFP) or a fusion.

(Ans. 6.)

Appellants contend that "there would [be] no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application" (App. Br. 11). In this regard, "Appellants particularly note that the first full paragraph of page 204 of Aran's disclosure states that when a retroviral vector encoding a wild type *Aequoria* [sic] GFP was introduced into in [sic] a mammalian cell, fluorescence was '***undetectable***'" (*id.*). Accordingly, Appellants contend that "Aran's disclosure, itself, teaches that the combination of Bryan and Aran would produce 'a seemingly inoperative' vector" (*id.* (footnote omitted)). We are not persuaded.

There is no requirement in Claim 1 that the retroviral vector express a protein that fluoresces in a mammalian cell (FF 1). In this regard, we note that Bryan teaches the expression of *Renilla* GFP for use in a wide variety of different applications, including those that do not require fluorescence in a mammalian cell (FF 7). To produce *Renilla* GFP, Bryan teaches that "[a]ppropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells . . . [including] those which integrate into the host cell genome" (e.g., a retrovirus) (FF 6). Appellants concede that retroviral vectors expressing GFP proteins (e.g., as taught by Aran) were well known in the art prior to Appellants' filing date (FF 3). Accordingly, a person of ordinary skill in the art would have found it prima facie obvious at the time of Appellants' claimed invention to make use of retroviral vectors to express *Renilla* GFP for any of the wide variety of applications taught by Bryan (FF 7). "The combination of familiar

elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1740.

Furthermore, Aran teaches that retroviral vectors encoding a mutant *Aequorea* GFP produced detectable fluorescence in the host cell (FF 3). Bryan teaches that "a stated purpose in constructing such [prior art] mutants has been to attempt to make the *A. Victoria* GFP more like the GFP from Renilla" (FF 4). Therefore, the prior art recognized that in order to obtain fluorescence of *A. Victoria* GFP in a host cell, a person of ordinary skill in the art modifies the *A. Victoria* GFP to make it more like *Renilla* GFP. For this reason, a person of ordinary skill in the art at the time of Appellants' claimed invention would have reasonably expected that a retrovial vector expressing *Renilla* GFP would have produced detectable fluorescence in a host cell. "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d at 1581 (internal quotations omitted). Accordingly, we are not persuaded by Appellants' contention to the contrary.

Aran, Bryan, and Zolotukhin:

Based on the combined teaches of Aran, Bryan, and Zolotukhin (FF 2-6) the Examiner concludes that

> it would have been prima facie obvious to one of ordinary skill at the time of Appellant's [sic] invention to modify the cellular/vector genetic constructs taught by the Aran and Bryant [sic] reference to include human codon-optimized (e.g., humanized) nucleotides encoding renilla [sic] GFP in order to obtain the advantages thereof as taught by . . . Zol[o]tukhin.

(Ans. 8.)

Appellants do not dispute and therefore concede that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the codons of a wild-type *Renilla* GFP polynucleotide (FF 2) to optimize its expression in human cells (FF 3 and 5). Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Instead, Appellants contend that "there would [be] no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application" (App. Br. 11). In this regard, "Appellants particularly note that the first full paragraph of page 204 of Aran's disclosure states that when a retroviral vector encoding a wild type *Aequoria* [sic] GFP was introduced into in [sic] a mammalian cell, fluorescence was '***undetectable***'" (App. Br. 12). We are not persuaded for the reasons set forth above with regard to the combination of Bryan and Aran.

Zolutokhin and Bryan:

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative (FF 1).

Based on the combined teachings of Zolotukhin and Bryan (FF 2-7) the Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time of appellant's [sic] invention to utilize the Bryan polynucleotide Renilla green fluorescent protein . . . in the Zol[o]tukhin . . . genetic constructs" (Ans. 11).

Appellants contend that "there would [be] no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application" (App. Br. 12). We are not persuaded.

There is no requirement in Claim 1 that the retroviral vector express a protein that fluoresces in a mammalian cell (FF 1). In this regard, we note that Bryan teaches the expression of *Renilla* GFP for use in a wide variety of different applications, including those that do not require fluorescence in a mammalian cell (FF 7). To produce *Renilla* GFP, Bryan teaches that "[a]ppropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells . . . [including] those which integrate into the host cell genome" (e.g., a retrovirus) (FF 6). Appellants concede that retroviral vectors expressing GFP proteins (e.g., as taught by Zolotukhin) were well known in the art prior to Appellants' filing date (FF 3). Accordingly, a person of ordinary skill in the art would have found it prima facie obvious at the time of Appellants' claimed invention to make use of retroviral vectors to express *Renilla* GFP for any of the wide variety of applications taught by Bryan (FF 7). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1740.

Furthermore, Zolotukhin teaches mutant versions of GFP genes adapted for high level expression in mammalian cells, such as those wherein base substitutions are made in order to change the codon usage to one more appropriate for expression in mammalian cells (FF 3). Zolotukhin also teaches that "[c]ertain GFP variants have recently been reported that have improved spectral properties[, specifically] a Ser 65 → Thr GFP mutant that has a spectrum much closer to that of *Renilla reniformis*, which has an extinction coefficient per monomer more than 10 times that of the longer-wavelength peak of Aequorea GFP" (*id.*). Bryan teaches that "a stated purpose in constructing such [prior art] mutants has been to attempt to make

the *A. Victoria* GFP more like the GFP from Renilla" (FF 4). Therefore, the prior art recognized that in order to obtain fluorescence of *A. Victoria* GFP in a host cell, a person of ordinary skill in the art modifies the *A. Victoria* GFP to make it more like *Renilla* GFP. For this reason, a person of ordinary skill in the art at the time of Appellant's claimed invention would have reasonably expected that a retrovial vector expressing *Renilla* GFP would have produced detectable fluorescence in a host cell. "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d at 1581 (internal quotations omitted). Accordingly, we are not persuaded by Appellants' contention to the contrary.

Bierhuizen and Bryan:

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative (FF 1).

Based on the combined teachings of Bierhuizen and Bryan (FF 2-7) the Examiner concludes that "it would have been prima facie obvious for an ordinary skilled artisan to . . . generate a retroviral vector comprising a polynucleotide encoding a GFP with a specific amino acid sequence (e.g., wildtype Renilla GFP amino acid sequence)" (Ans. 16).

Appellants contend that "there would [be] no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application" (App. Br. 12). In this regard, Appellants assert that "Bierhuizen notes that at 24 hours after transduction, wild type GFP expression is extremely weak compared to cells expressing mutant GFP"

(*id.*). From this Appellants contend that "Bierhuizen fails to report stable cell lines that express wild type *Aequoria* GFP. Given the teachings of Aran, Hanzano, Levy, Cheng and Anderson . . . such cell lines would be impossible to make" (App. Br. 13). We are not persuaded.

There is no requirement in Claim 1 that the retroviral vector express a protein that fluoresces in a mammalian cell (FF 1). Further, there is no requirement in Claim 1 that requires the claimed retroviral vector be used to produce a stable cell line that expresses a green fluorescent protein (GFP) having the amino acid sequence of SEQ ID NO: 2 (*id.*). In this regard, we note that Bryan teaches the expression of *Renilla* GFP for use in a wide variety of different applications, including those that do not require fluorescence in a mammalian cell or a stable cell line that expresses a green fluorescent protein (GFP) having the amino acid sequence of SEQ ID NO: 2. (FF 7). To produce *Renilla* GFP, Bryan teaches that "[a]ppropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells . . . [including] those which integrate into the host cell genome" (e.g., a retroviral vector) (FF 6). Appellants concede that retroviral vectors expressing GFP proteins (e.g., as taught by Bierhuizen) were well known in the art prior to Appellants' filing date (FF 3).

Accordingly, a person of ordinary skill in the art at the time of Appellants' claimed invention would have found it prima facie obvious to make use of retroviral vectors to express *Renilla* GFP for any of the wide variety of applications taught by Bryan (FF 7). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1740.

Furthermore, Bierhuizen teaches "retroviral vectors containing the *Aequorea Victoria* green fluorescent protein (GFP) gene and improved versions thereof" (FF 3). Bryan teaches that "a stated purpose in constructing such [prior art] mutants has been to attempt to make the *A. Victoria* GFP more like the GFP from Renilla" (FF 4). Therefore, the prior art recognized that in order to obtain fluorescence of *A. Victoria* GFP in a host cell, a person of ordinary skill in the art modifies the *A. Victoria* GFP to make it more like *Renilla* GFP. For this reason, a person of ordinary skill in the art at the time of Appellants' claimed invention would have reasonably expected that a retrovial vector expressing *Renilla* GFP would produce detectable fluorescence in a host cell. "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d at 1581 (internal quotations omitted). Accordingly, we are not persuaded by Appellants' contention to the contrary.

For the foregoing reasons the teachings of Aran, Hanzano, Levy, Cheng and Anderson do not support Appellants' contentions (*see* App. Br. 13).

Bierhuizen, Bryan, and Aran:

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative (FF 1).

For the reasons set forth above, it would have been prima facie obvious to utilize a polynucleotide encoding Bryan's *Renilla* GFP in a retroviral vector as taught by Bierhuizen and Aran (FF 2-7).

Appellants contend that "there would [be] no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application" (App. Br. 13). In this regard, "Appellants particularly note that the first full paragraph of page 204 of Aran's disclosure states that when a retroviral vector encoding a wild type *Aequoria* [sic] GFP was introduced into in [sic] a mammalian cell, fluorescence was '***undetectable***'" (*id.*). We are not persuaded for the reasons set forth above with regard to the combination of Bryan and Aran. In addition, Appellants assert that Bierhuizen "is a single reference in a field in which many others report repeated failure" and "reports only marginal results [with] their vector" (*id.*). We are not persuaded for the reasons set forth above with regard to the combination of Bierhuizen and Bryan.

Anderson and Bryan:

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative (FF 1).

Based on the combined teachings of Anderson and Bryan (FF 2-7) the Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time of Appellants' claimed invention to utilize a polynucleotide encoding Bryan's *Renilla* GFP in a retroviral vector as taught by Anderson (*see e.g.*, Ans. 18).

Appellants contend that "there would [be] no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application" (App. Br. 14).

> Appellants particularly note that Anderson states in the background section that suboptimal excitation spectra of wild type GFP "*precludes the detection of wtGFP* when a single

> copy of the gene is stably integrated", and in the first paragraph of the results section, with reference to a population of cells infected with a retroviral vector encoding wild type *Aequoria* [sic] GFP, states: "the difference in *fluorescence was not sufficient* to resolve infected from uninfected cells[.]"

(*Id.*) We are not persuaded.

There is no requirement in Claim 1 that the retroviral vector express a protein that fluoresces in a mammalian cell (FF 1). In this regard, we note that Bryan teaches the expression of *Renilla* GFP for use in a wide variety of different applications, including those that do not require fluorescence in a mammalian cell or a stable cell line that expresses a green fluorescent protein (GFP) having the amino acid sequence of SEQ ID NO: 2. (FF 7). To produce *Renilla* GFP, Bryan teaches that "[a]ppropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells . . . [including] those which integrate into the host cell genome" (FF 6). Appellants concede that retroviral vectors expressing GFP proteins (e.g., as taught by Anderson) were well known in the art prior to Appellants' filing date (FF 3).

Accordingly, a person of ordinary skill in the art would have found it prima facie obvious at the time of Appellants' claimed invention to make use of retroviral vectors to express *Renilla* GFP for any of the wide variety of applications taught by Bryan (FF 7). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1740.

Furthermore, Anderson teaches *Aequorea Victoria* GFP variants that "includ[e] the S65T and V163A mutations (termed GFP-Bex1)" and that their "studies show that GFP-Bex1 . . . have sufficient fluorescence signal to

be readily detected by FACS, and that both variants can be quantitatively detected independently, permitting their simultaneous detection at the single cell level" (FF 3). Bryan teaches that "a stated purpose in constructing such [prior art] mutants has been to attempt to make the *A. Victoria* GFP more like the GFP from Renilla" (FF 4). Therefore, the prior art recognized that in order to obtain fluorescence of *A. Victoria* GFP in a host cell, a person of ordinary skill in the art modifies the *A. Victoria* GFP to make it more like *Renilla* GFP. For this reason, a person of ordinary skill in the art at the time of Appellants' claimed invention would have reasonably expected that a retrovial vector expressing *Renilla* GFP would produced detectable fluorescence in a host cell. "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d at 1581 (internal quotations omitted). Accordingly, we are not persuaded by Appellants' contention to the contrary.

CONCLUSION OF LAW

Detectable fluorescence in a mammalian cell is *not* necessary to render the claimed invention prima facie obvious to a person of ordinary skill in the art at the time the invention was made in view of the combination of references relied upon by the Examiner.

The rejection of Claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Bryan and Aran is affirmed. Claims 2, 3, and 20 fall together with claim 1.

The rejection of Claim 20 under 35 U.S.C. § 103(a) as unpatentable over the combination of Aran, Bryan and Zolotukhin is affirmed.

The rejection of Claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Zolotukhin and Bryan is affirmed. Claims 2, 3, and 20 fall together with claim 1.

The rejection of Claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Bierhuizen and Bryan is affirmed. Claims 3 and 20-22 fall together with claim 1.

The rejection of Claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Bierhuizen, Bryan and Aran is affirmed. Claims 2, 3, and 20-22 fall together with claim 1.

The rejection of Claims 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Anderson and Bryan. Claims 3 and 20-22 fall together with claim 1.

Time Period For Response

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

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